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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/026,188	12/21/2001	Charles S. Zuker	02307E-114910US	9521

20350 7590 04/18/2006

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 04/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/026,188	ZUKER ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,12 and 14-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-9, 12, 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on February 2, 2006 have been entered in full.

Response to Amendment

Applicant is notified that any outstanding rejection that is not explicitly maintained in this Office Action has been withdrawn in view of Applicant's amendments and persuasive arguments. Applicant is reminded that the claims will be examined only to the extent that they read on the elected SEQ ID NO: 8.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-9, 12, 14-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require either methods of identifying a compound that modulates taste signaling (claim 1) or methods of modulating taste signaling. The words "modulates" and "modulating" in the claims render the claims indefinite because the words are indefinite terms and neither the claim nor the specification sets forth what physical processes are intended to be encompassed in the scope of the term and what are not, thus the metes and bounds of the claim cannot be determined. At page 11, last paragraph, of the specification the word "modulates" is

distinguished from the words "inhibitors" and "activators" yet no definition is provided that sets forth what properties distinguishes a modulator from and activator or inhibitor. Thus the artisan could not understand the meaning of the term and could therefore not be able to determine the meets and bounds of the claim.

Applicant argues that "modulate" includes various inhibitors, activators, etc. This argument has been fully considered but not deemed persuasive. These examples are insufficient to establish was is, and what is not, to be considered to be circumscribed by the claims.

Applicant argues that a common definition of "modulate" includes "change", as disclosed by thesaurus.com. This argument has been fully considered but not deemed persuasive. Applicant is reminded that other synonyms for modulate, as provided by thesaurus.com, include "attune, balance, do up, fine tune, harmonize, inflect, regulate, restrain, revamp, switch, temper, tone, transmogrify, tune, tweak, vary, yo-yo"; these terms provide further evidence of the indefiniteness of the term and do not define the bounds of the term nor the claims.

Applicant's amendments to claims 1 and 12 have clarified what "functional effect" is to be measured, however the amendments contain the phrase "wherein the functional effect is under the influence of the taste cell-specific ion channel subunit" it unclear what is meant by "under the influence". The artisan can not determine what additional limitations are placed on the claim by the presence of this phrase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-9, 12, 14-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification proposes that at least on of SEQ ID NO: 2, 5, and 8 are taste receptors that modulate taste perception. Also proposed are a multitude of assays, used in the art to study particular biochemical pathways involved with different aspects taste signal transduction as well as signal transduction in general, see pages 23-28. Yet in order to practice the invention as claimed, one skilled in the art would need to know which of these assays and which materials, could be used in conjunction with the polypeptide of SEQ ID NO: 8. The specification admits that it is well recognized in the art that the signal transduction schemes underlying taste transduction are bewilderingly complex and poorly understood, page 3. Thus, at best, at the time of filing one of skill in the art would expect that to carry out an extensive research plan to try to use the invention as claimed, if that can be done, would be unduly burdensome.

Applicant challenges the above assertion regarding the bewilderingly complexity and poorly understood state of the art regarding taste transduction. This argument has been fully considered but not deemed persuasive. The statement was a paraphrase of the discussion in the

specification which clearly testifies to the bewilderingly complexity and poorly understood state of the art regarding taste transduction.

Applicant argues that much is known about ion channels in general. This argument has been fully considered but not deemed persuasive. The specification merely presents a laundry list of examples of the behavior of previously characterized ion channels. However, specific details regarding the particular channel in question are need to practice the invention. Such details are lacking.

Additionally, claims 1 and 17 require the step of forming a functional ion channel, yet the specification has not disclosed what steps to follow to determine if a functional channel has been formed. The specification does not teach what ligand would open the channel so that one could measure the ion flux so as to know that it is functional.

Applicant argues that the specification has provided assays that the artisan could use to determine the functional effect of the ion channel. This argument has been fully considered but not deemed persuasive. As set forth above, the specification simply presents the artisan with a list of experiments that could be tried to find a functional effect. This amounts to nothing more than an invitation to perform further research and investigation in the hope of discovering how to make the invention.

Furthermore, claims 12, 14-15 require compounds that directly modulate the activity of the polypeptide of SEQ ID NO: 8. There is no teaching of compounds that directly modulate the activity of the polypeptide of SEQ ID NO: 8 and one of skill in the art would view the invitation to randomly sample chemicals in the hope of finding such would be unduly burdensome.

Applicant argues that the claims have been reworded to allow selection of the compounds. This argument has been fully considered but not deemed persuasive. The claims still require compounds that are not taught.

Additionally, the claims are directed to the use of amino acid sequence variants of SEQ ID NO: 8; *should* Applicant establish that the specification is enabling for assays to measure modulation of taste signaling as claimed with regard to SEQ ID NO: 8, the specification has failed to teach which amino acid substitutions should be made in SEQ ID NO: 8 so as to preserve any function of SEQ ID NO: 8, as discussed previously.

Applicant argues that the specification has provided alignments of three polypeptide to guide the artisan to make conservative substitutions and that the expectation that such conservatively modified variants would be functional is quite high. This argument has been fully considered but not deemed persuasive. Applicant is referred to Bowie et al. at page 1308, col 1, last paragraph. Bowie teaches "Functionally important residues should be conserved in sets of active sequences, bit it is not possible to decide whether a side chain is functionally or structurally important just because it is invariant or conserved. To make this distinction requires an independent assay of protein folding". No evidence has been put fourth to support Applicant's argument or refute the teachings of Bowie et al. referred to above and the analysis made in the rejection. Arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See In re Budnick, 537 F.2d at 538, 190 USPQ at 424; In re Schulze, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); In re Cole, 326 F.2d 769, 140 USPQ 230 (CCPA 1964).

Furthermore, the claims encompass an astronomical number of artificially constructed variants of the naturally occurring SEQ ID NO: 8. The instant polypeptide (SEQ ID NO: 8) is disclosed as being 1165 amino acids in length; thus a polypeptide having 90% identity with SEQ ID NO: 8 would have at least 116 amino acid substitutions relative to SEQ ID NO: 8. Regarding the advanced state of the art, Applicant is referred to Guo et al. PNAS 101(9205-9210)2004 wherein the authors completed a systematic study of the tolerance that natural proteins have to amino acid sequence change. They found that on average a single amino acid replacement had a 34% chance of inactivating a protein, see the Abstract. Thus, one skilled in the art the would not expect that a substantial number of variants that contained 116 amino acid substitutions would retain functionality, even if the functionality were known.

While it may be true that functional variants typically contain only conservative variation or variation in non-critical resides or non-critical regions, this teaching does not provide any information as to where these sites of conservative variation, non-critical residues, or non-critical regions could be - such information being necessary to enable the skilled artisan to make and use the claimed invention without undue experimentation. Further, the specification failed to provide guidance as to what any particular functional property of the claimed polypeptide is; nor any particular functional difference between the polypeptide and sequence variants of the polypeptide. Thus, one of skill in the art would not know how to create a variant of a polypeptide having a particular function if that function was not known nor if there were no teachings as to how to produce that function, e.g. agonist binding, so as to test the variants for functionality.

Claims 1, 3-9, 12, 14-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments, paragraphs 1 and 2 of page 13 of the 2/2/06 response, regarding the assay methods are persuasive.

However, claims 1, 12, 17 require the step of forming a functional ion channel, yet the specification has not disclosed what steps to follow to determine if a functional channel has been formed. The specification does not teach what ligand would open the channel so that one could measure the ion flux so as to know that it is functional. There is no evidence in the specification that demonstrates that Applicant either produced a functional ion channel or know how to produce a functional ion channel with SEQ ID NO: 8. Thus one skilled in the art would not view that Applicant was in possession of the claimed invention.

Applicant's arguments regarding the teaching of a functional effect have been substantially addressed above. There is no evidence that Applicant was in possession of a functional ion channel.

Furthermore, claims 12, 14-15 require compounds that directly modulate the activity of the polypeptide of SEQ ID NO: 8. There is no teaching of compounds that directly modulate the activity of the polypeptide of SEQ ID NO: 8, thus there is no evidence Applicant was in possession of such. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be

unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant argues that the claims have been amended to obviate the rejection. This argument has been fully considered but not deemed persuasive. The claims require compounds that one skilled in the art would not recognize that applicant was in possession of.

Additionally, the specification discloses the polypeptide of SEQ ID NO: 8 yet the claims encompass assays involving an essentially limitless genus of polypeptides not described in the specification, i.e. polynucleotides sequences from other species, mutated sequences, allelic variants, and sequences that need only 90% identity with SEQ ID NO: 8. yet which retain the required functional limitations. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist or could exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of three polynucleotides does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, only one sequence at least

90% identical to SEQ ID NO: 8, which is SEQ ID NO: 8 itself, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

With the exception of polynucleotides encoding polypeptides of SEQ ID NO: 8 referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed variants and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only the polypeptide of SEQ ID NO: 8, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant argues that an alignment of sequences provides structural information that can that satisfies the requirements of *Lilly*. This argument has been fully considered but not deemed persuasive. There appear to be know teachings of structural features that are definitive of the genus of polypeptides that are 90% identical to SEQ ID NO: 8 and retain any functional property.

Applicant argues that the specification teaches methods for verifying the function of an ion channel. This argument has been fully considered but not deemed persuasive. One skilled in the art would view the broad teachings of pages 23-28 as simply a survey of general methods of

studying signal transduction and not as specific instructions to be used to verify the functionality of a polypeptide of SEQ ID NO: 8, e.g. no ligand or activator of the polypeptide is taught. Thus, one could not know whether the channel was functional unless a ligand is discovered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-6, 8, 12, 14, 16, 17 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Publication 2002/0037515, published March 28, 2002, which is fully supported by prior provisional application, US 60/197,491, filed April 17, 2000, as set forth previously and reiterated below.

US Patent Publication 2002/0037515 discloses a polypeptide TRP8 that is identical to the instant SEQ ID NO: 8 with the two exceptions that the glutamine at position 630 is missing in TRP8 and threonine is substituted for Aspartic acid at position 990. Never-the-less, TRP8 is asserted to be a taste-cell receptor protein that modulates taste transduction, see the Abstract. The production of Antibodies is disclosed (paragraph 0049) and taught to be used in screening assays to identify modulators of taste transduction see section 5.5. Further, US Patent

Publication 2002/0037515 discloses a particular voltage clamp assay that measures the effect of modulators on Calcium mediated activation of the TRP8, see section 6.2.5.

Methods of using these identified modulators to modulate taste signaling in humans are also contemplated, e.g. paragraph 10.

Applicant argues that the 1.131 Declaration (Drs. Zuker and Zhang) asserts that the claimed invention was completed before the filing date of US 60/197,491, filed April 17, 2000. This argument has been fully considered but not deemed persuasive. 37 CFR1.131(a)1 requires that the oath or declaration must include facts showing a completion of the invention. It appears that the Declaration simply asserts possession of a clone (clone 501) before April 17, 2000. This clone is asserted to be one of three that make up contig No. 068-3 157 501, and this contig is listed as being 629 base pairs in length. The instant SEQ ID NO: 8 consists of 1165 amino acids, and thus the minimum length required to encode it is 3495 base pairs. Contig No. 068-3 157 501 is less than 20% of this required length. Thus the Declaration does not establish that applicant completed the claim invention prior to April 17, 2000.

Applicant argues that Applicant was in possession of the sequences prior to April 17, 2000. This argument has been fully considered but not deemed persuasive. Arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See In re Budnick, 537 F.2d at 538, 190 USPQ at 424; In re Schulze, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); In re Cole, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). The Declaration does not appear to of the same scope as argued by counsel.

Claims 1, 3, 4 are rejected under 35 U.S.C. 102(anticipated) as being anticipated by the Abstract of Bernhardt-SJ et al., J. Physiol. 490(325-336)1996, who disclose a method of identifying a compound (e.g. sucrose) that modulates taste signaling in taste cells comprising contacting the compound with a eukaryotic host cell (rat circumvallate cells) which would be expected to express a polypeptide at 90% identical to the instant SEQ ID NO: 2 (which is disclosed as being from a rat) and would form a functional channel absent evidence to the contrary, and determining a functional effect (changes in intracellular calcium concentration) using ion sensitive dyes (e.g. Ca^{2+} imaging). It is noted that the claims do not require that the transmembrane ion flux be that of either SEQ ID NO: 2, 5, 8, rather this influx could be the Ca^{2+} influx into the cytoplasm from intracellular stores - which is what is detected by Bernhardt-SJ et al.

Applicant argues that the reference does not teach that the functional effect is under the influence of the taste cell-specific ion channel subunit. This argument has been fully considered but not deemed persuasive. A polypeptide of SEQ ID NO: 2 is expressed in rat circumvallate cells and would thus be an inherent feature, absent evidence to the contrary.

Claims 1, 2, 4-7are rejected under 35 U.S.C. 102(anticipated) as being anticipated by Doolin-RE et al., J. Gen Physiol 107(545-554)1996 who disclose a method of identifying a compound (e.g. amiloride, see Fig 4) that modulates taste signaling in taste cells comprising contacting the compound with a eukaryotic host cell (rat circumvallate cells, see fig 4) which would express a polypeptide at 90% identical to the instant SEQ ID NO: 2 (which is disclosed as being from a rat) and would form a functional channel absent evidence to the contrary, and determining a functional effect either as changes in intracellular ion concentration and ion flux (whole-cell

recording), and where the membrane is attached to a solid support e.g. pipette (patch pipette technique), page 547.

Applicant argues that the reference does not teach that the functional effect is under the influence of the taste cell-specific ion channel subunit. This argument has been fully considered but not deemed persuasive. A polypeptide of SEQ ID NO: 2 is expressed in rat circumvallate cells and would thus be an inherent feature, absent evidence to the contrary.

Conclusion

This application contains claims 1, 3-9, 12, 14-17 are drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX months.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

April 17, 2005